

ABSTRACT

Chimeric oligonucleotide of the formula 5'-W-X<sup>1</sup>-Y-X<sup>2</sup>-Z-3', where W represents a 5'-O-alkyl nucleotide, each of X<sup>1</sup> and X<sup>2</sup> represents a block of seven to twelve phosphodiester-linked 2'-O-alkyl ribonucleotides, Y represents a block of five to twelve phosphorothioate-linked deoxyribonucleotides, and Z represents a blocking group effective to block nuclease activity at the 3' end of the oligonucleotide, are described. These compounds exhibit high resistance to endo- and exonucleases, high sequence specificity, and the ability to activate RNase H, as evidenced by efficient and long-lasting suppression of target mRNA. The oligonucleotides are preferably transfected into cells in formulations containing a lipid-peptoid conjugate carrier molecule of the formula

L-linker-[N(CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>)CH<sub>2</sub>(C=O)-N(CH<sub>2</sub>CH<sub>2</sub>R)CH<sub>2</sub>(C=O)-N(CH<sub>2</sub>CH<sub>2</sub>R)CH<sub>2</sub>(C=O)]<sub>3</sub>-NH<sub>2</sub>,

where L is a lipid moiety, including a steroid, and each group R is independently selected from alkyl, aminoalkyl, and aralkyl.